AMENDMENT

In the Specification:

Please amend the specification on page 56 as follows:

C1

(At line 4:) 5' primer 5'-TGGGATTACACGTGTGAACAACC-3' (SEQ ID NO: 1)

(At line 5:) 3' primer 5'-GATCCACAGTCTGCCTGAGTCACT-3' (SEQ ID NO: 2)

C2

(At line 10:) nested 5' primer: 5'-CCTAGAAAGCACATGGAGAGCTAG-3' (SEQ ID NO: 3)

RESPONSE

1. Sequence ID Identifiers

The specification has been objected to for lacking sequence identifiers. Applicants have amended the specification to comply with the sequence identifier requirement and thus respectfully request withdrawal of the objection.

2. Sequence Listing

The Office Action had required a sequence listing in computer readable form as well as a paper copy, an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and include no new matter. Applicants hereby respectfully submit both a computer readable sequence listing and a paper copy thereof. The content of the paper and computer readable copies are the same and include no new matter.

3. The Invention

The present invention relates to methods for overcoming the resistance of cancer cells to chemotherapy and radiation. The present invention is based on the discovery that cell death can be induced in cancer cells that are otherwise refractory to chemotherapy and radiation by the inhibition of their DNA repair mechanisms. The significance of the present invention lies in the fact that even highly malignant types of cancer no longer have to be considered invariably fatal, but may be rendered amenable to effective treatment. Highly malignant tumors are characterized by extensive DNA damage which may be the result of intrinsically high levels of karyotypic instability typical of malignant

tumor cells or it may be induced by DNA damaging agents, such as those used in cancer chemo- and radiation therapies. These malignant cells have evolved mechanisms which enable them to survive levels of DNA damage that would be lethal in normal or less malignant cell types. One of the mechanisms used by malignant cells to overcome the lethality of extensive DNA damage is the upregulation of DNA repair. The present invention shows that inhibition of DNA repair pathways in tumor cells containing damaged DNA effectively kills previously nonresponding cancer cells and offers new hope for cancer patients with poor prognoses due to advanced disease stage, development of recurrent chemotherapy resistant tumor, or highly malignant cancer types.

4. <u>The Invention Is Not Anticipated Under 35 U.S.C. §102</u>

The Office Action rejected claims 1, 6-9, and 18-26 under 35 U.S.C. §102(e) as being anticipated by Roth et al. (U.S. Patent No. 6,069,134) as evidenced by Jones et al. (Mutation Research, DNA Repair, 1991, Vol. 255, pages 155-162). The Office Action stated that "Roth *et al.* teach a method of treating a human subject wherein said subject has cancer (including lung, breast, colon; column 7, lines 45+) further including squamouse carcinomas (column 13, line 33), sarcomas, or melanomas (column 38, lines 34+) comprising introducing into said cell an expression construct comprising a nucleic acid segment encoding p53 and a promoter operably linked to said nucleic acid segment, **and contacting said cell with at least one inhibitory agent that inhibits DNA repair** wherein said expression construct is an adenoviral expression construct (abstract, and column 6, lines 40+)..." Applicants respectfully traverse. The Roth patent is directed exclusively to methods of killing tumor cells by delivering p53 to the tumor cells and

contacting the tumor cells with DNA damaging drugs. Nowhere does the Roth patent disclose, claim, or suggest treating tumor cells by inhibiting DNA repair.

According to the Office Action "Roth et al. further teach that p53 may be used in combination with a chemotherapeutic agent such as camptothecin (column 9, line 26)," and referring to Jones *et al.* "camptothecin is an inhibitory agent that inhibits DNA repair, wherein camptothecin inhibits topoisomerase I (abstract; Table 2, page 159; and page 160, 2nd column, 3rd paragraph). Applicants respectfully point out that the Roth patent correctly characterizes camptothecin as a DNA damaging drug:

> **DNA damaging agents or factors are defined herein as any chemical compound or treatment method that induces DNA damage when applied to a cell.** Such agents and factors include radiation and waves that induce DNA damage, such as, .gamma.-irradiation, X-rays, UV-irradiation, microwaves, electronic emissions, and the like. A variety of chemical compounds, also described as **"chemotherapeutic agents", function to induce DNA damage**, all of which are intended to be of use in the combined treatment methods disclosed herein. Chemotherapeutic agents contemplated to be of use, include, e.g., adriamycin, 5-fluorouracil (5FU), etoposide (VP-16), **camptothecin**, actinomycin-D, mitomycin C, cisplatin (CDDP), and even hydrogen peroxide. The invention also encompasses the use of a combination of one or more DNA damaging agents, whether radiation-based or actual compounds, such as the use of X-rays with cisplatin or the use of cisplatin with etoposide. In certain embodiments, the use of cisplatin in combination with a p53 protein or gene is particularly preferred as this compound.

(See Roth US Patent No. 6,069,134 column 4, line 57, to column 5, line 8).

Further:

> In treating cancer according to the invention one would contact the tumor cells with a **DNA damaging agent** in addition to the p53 protein or gene. This may be achieved by irradiating the localized tumor site with DNA damaging radiation such as X-rays, UV-light, .gamma.-rays or even microwaves. Alternatively, the tumor cells may be contacted with the DNA damaging agent by administering to the animal a therapeutically effective amount of a pharmaceutical composition comprising a **DNA damaging compound**, such as, adriamycin, 5-fluorouracil, etoposide, **camptothecin**, actinomycin-D, mitomycin C, or more preferably, cisplatin. The DNA damaging agent may be prepared and used as a combined therapeutic composition, or kit, by combining it with a p53 protein, gene or gene delivery system, as described above.

(See Roth US Patent No. 6,069,134 column 8, lines 10 to 24).

And:

> Preferred pharmaceutical compositions of the invention are those that include, within a pharmacologically acceptable solution or buffer, a p53 protein, or more preferably a p53 gene, in combination with a **chemotherapeutic DNA damaging agent. Exemplary chemotherapeutic agents are** adriamycin, 5-fluorouracil, **camptothecin**, actinomycin-D, hydrogen peroxide, mitomycin C, cisplatin (CDDP), and etoposide (VP-16), with the use of cisplatin being particularly preferred.

Thus, while the Roth patent discloses DNA damaging agents to be used in conjunction with p53 to induce apoptosis in certain tumor cells, it fails to disclose the method of the present invention, i.e. inhibition of DNA repair as a strategy to overcome tumor resistance to DNA damaging therapy. Applicants further point out that Jones et al. generically identify camptothecin as a topoisomerase I inhibitor and speculate that topoisomerase I may be involved in total genomic repair due to an observed weak inhibition of overall genomic repair by camptothecin that contrasts with the results obtained by other groups (p. 160, second column, third paragraph). Indeed, as the scientific understanding of the molecular mechanism of action of camptothecin has advanced in the years after the Jones publication (1991), it has become firmly established in the art that camptothecin is a DNA damaging agent that acts by "poisoning" topoisomerase I after the topoisomerase catalyzes the first strand break and before religation of the strand. The resulting complex between cleaved DNA and topoisomerase I interferes with both DNA transcription and replication through collision with RNA and DNA polymerases, leading to severe cytotoxicity and cell death. Thus, instead of inhibiting any DNA repair mechanism, camptothecin acts to induce DNA lesions. By contrast, the DNA repair inhibitors contemplated by the present invention act only at the next step: after DNA damage has occurred and the cancer cell begins to mobilize the enzymes responsible for repairing the DNA damage it has sustained. Because

camptothecin acts at the step of DNA damage which precedes the DNA repair step it is properly excluded from the definition of DNA repair inhibitors according to the present invention. Thus, neither the Roth patent nor the Jones reference anticipate the method of inhibiting DNA repair to which the present invention is directed.

It is respectfully submitted that all pending claims are patentable to applicants over the prior art and an early allowance is earnestly sought.

Respectfully submitted,
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